REMARKS

Amendments to the Specification

The specification has been amended to insert the section header Brief Description of the Figures, including figure legends as requested by the Examiner. Also, the Abstract has been amended as requested to more accurately reflect the invention as claimed.

The specification has additionally been amended to insert section headers for Field of the Invention, Background of the Invention, Summary of the Invention, Detailed Description of the Invention, and Examples.

The specification has been amended at pages 4, 5, 8, and 9 to change subscript variable N with n appearing in formulas (1) and (2). The Applicants are grateful to the Examiner for pointing out this much-regretted typographical error.

The Applicants respectfully request entry of the amendments to the specification and aver that the requested amendments to the specification do not introduce new matter.

Amendments to the Claims

Claim 2 has been extensively amended and these amendments will be addressed in turn. First, element a) has been amended to remove cyclosporins and insert "one or more hydrophobic active ingredients". A weight range for component a) of the formulation has also been added to this claim element. Support for these amendments may be found in the specification at, for example, page 6, last paragraph and Examples 1-10.

Element b) of claim 2 has been amended to change the percentage of component b) in the formulation and placing the limitation that at least one of the R group substituents have an HLB value of not less than 10. Support for these amendments may be found at page 9, 2nd full paragraph, and formulation Examples 1 – 17.

Element c) of claim 2 has been amended to change the percentage of component c) in the formulation and placing the limitation that at least one of the R group substituents have an HLB value no greater than 9. Additionally, this element has been amended to limit element c) to polyglyceryl-3-esters of oleic acid. Support for this amendment may be found

in the specification at, for example, page 9, 2nd full paragraph, and formulation Examples 1 – 7 and 9 – 17.

Element d) of claim 2 has been amended to change the percentage of component d) in the formulation. Support for this amendment may be found at, for example, the formulation of Example 1.

Element e) has been added to claim 2 to better define the invention. Support for this amendment may be found at Examples 1 – 7.

Claims 25, 27, and 29 have been amended to change their dependency in order that they may be moved to follow new claim 41, upon allowance of the case.

Claim 31 has been canceled as the subject matter of claim 31 appears in amended claims 33 and 34. The amendment to these claims additionally amends the dosage form to a pharmaceutical dosage form comprising the formulation of claim 2 in combination with a pharmaceutically acceptable excipient, as suggested by the Examiner. Support for these amendments may be found, for example, in Examples 1 – 3.

The Applicants respectfully request entry of the amendments to the claims and aver that the requested amendments do not introduce new matter.

The Specification as Amended Satisfies 35 U.S.C. § 112, First Paragraph

Claims 2, 25, 27, 29, 31, 33, and 34 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Applicants respectfully traverse this rejection.

The Examiner at page 3 of the Action, points to the last two lines of claim 2 where it is stated "upon dilution with any amount of water, a dispersion is formed in which the mean size of the particles is within the range of 0.2 to 500 μm." The Examiner is of the opinion that there is no descriptive support for the quoted language and requests, on page 4 of the Action that the Applicants point to the passage the meets the requirements of a) the

range of 0.2 to 500 μm is obtained regardless of the amount of water used, and b) the range of 0.2 to 500 μm is obtained when no alcohol is present.

The Examiner is directed to Example 19 of the specification to provide support for the particle size range produced when the composition is diluted with water. The first paragraph of the Example states:

> "[d]ifferent shapes of particles can be obtained by dispersal of formulations disclosed in this application. The following compositions when diluted gave dispersions of polymorphous gel particles. The visualization technique was as described in Example 5."

The Applicants respectfully submit that the dilution of the composition with water to produce polymorphous gel particles is implicit from the paragraph cited *supra*, when read in light of the claims as amended wherein "... compositions when diluted..." must refer to dilution with water.

Further note that the Examiner's request for support for b) the range of 0.2 to 500 μm is obtained when no alcohol is present, has been addressed by the amendment to claim 2, wherein element e), C_{2-4} alcohols, has been added to the claim.

The Applicants submit that the amendment to claim 2 (and claims dependent therefrom), in conjunction with the arguments presented *supra*, satisfies 35 U.S.C. § 112, first paragraph and respectfully request withdrawal of this rejection.

The Specification as Amended Satisfies 35 U.S.C. § 112, Second Paragraph

Claims 2, 25, 27, 29, 31, 33, and 34 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the inventions. The Applicants respectfully traverse these rejections and will address each rejection in turn below.

The Examiner has rejected claim 2 citing that the "average quantity of reacted ethylene oxide ... ranges between 50 to 150 mols" is not particularly meaningful as such. The Examiner then proposes the example of carrying out the reaction on a 1 gram scale, thereafter stating that only about 23 millimoles of ethylene oxide would be present.

The Applicants submit that the claim is clear on its face where the element reads " 1.0 to 60 % by weight of one or more co-gelator substances selected from the group consisting of triglyceride macrogol glycerol esters, partial glycerides of fatty acids and macrogol esters of fatty acids in which the average quantity of reacted ethylene oxide in the synthesis of the substances ranges between 50 to 150 mols and concurrently the ratio between components b) and d) is from 0.1:1 to 10:1. (Emphasis added). The quantity of reacted ethylene oxide cited in the claim refers to the amount used in the synthesis of the triglyceride macrogol glycerol esters, partial glycerides of fatty acids and macrogol esters of fatty acids and not to the amount of ethylene oxide present in the formulations of the invention. The Applicants submit that claim 2, with amendments satisfies 35 U.S.C. § 112, second paragraph and respectfully request withdrawal of this rejection.

The Examiner has also rejected claim 2 stating that it is unclear whether the ratio between components b) and d) referred to in the claims is determined on the basis of weight or moles. Claim 2 has been amended *supra*, to incorporate "by weight" into the claim elements. The Applicants submit that claim 2, with amendments, satisfies 35 U.S.C. § 112, second paragraph and respectfully request withdrawal of this rejection.

Claim 27 has been rejected in that claim 27 permits a taxane to be present, which is neither required nor suggested by claim 2. Element a) of claim 2 has been amended *supra*, to include "0.1 to 30.0 % of one or more hydrophobic active ingredients", wherein hydrophobic elements encompasses taxanes. The Applicants submit that claim 27, taken with the amendments to claim 2 satisfies 35 U.S.C. § 112, second paragraph and respectfully request withdrawal of this rejection.

Finally, the Examiner has rejected claim 31 stating that the claim implicitly mandates an additional component beyond those recited in claim 2 be present, and that the nature of this additional component is not indicated in the claim. The Applicants point out that claim 31 has been cancelled in light of amended claims 33 and 34, which have incorporated the suggestions put forth by the Examiner. The Applicants submit that cancelled claim 31, taken with the amendments to claims 33 and 34, satisfies 35 U.S.C. § 112, second paragraph and respectfully request withdrawal of this rejection.

The Specification as Amended Satisfies 35 U.S.C. § 103

Claims 2, 25, 27, 29, 31, 33, and 34 stand rejected under 35 U.S.C. § 103 as being unpatentable over Stuchlik, *et al.* (WO 98/10747, hereinafter "'747"). The Examiner contends that Stuchlik discloses compositions comprising cyclosporin and polyglycerol esters, and that while the reference does not disclose specific ratios of components, that it is in the capability of the ordinarily skilled drug formulation specialist to vary dosages in order to achieve a target pharmacokinetic objective. The Applicants respectfully traverse this rejection.

The '747 disclosure is directed to pharmaceutical compositions which create lyotropic liquid crystals when in contact with an aqueous phase. By definition, all liquid crystals have a common feature in that the crystals are all anisotropic. The Examiner is directed to page 6, 1st paragraph of the instant invention which states in summary that high bioavailability of cyclosporins and taxanes can be achieved following oral administration using a system that neither based on liquid crystals nor microemulsions. Unlike '747 where the crystals are spherical in nature, the Applicants unexpectedly found that the particles formed on mixing of the phases of the instant invention have a non-spherical character and show no sign of anisotropic grouping of the molecules. The particles that are formed have gel-like properties and, lacking anisitropicity, cannot be considered lyotropic liquid crystals.

Additionally, a comparison between Example 18 of the instant disclosure with Examples 11 and 13 of '747 indicates that the formulations of the instant invention provide greater bioavailability than those of '747.

The Applicants submit that the amendments to claim 2, for example, the differing requirements of HLB values for components b) and c), taken in conjunction with the observations and remarks presented *supra*, describe a distinctly different invention from that presented in '747. The Applicants further submit that it would require more than mere formulation optimization of '747 to produce a non-lyotropic liquid formulation with enhanced bioavailability. As such, the Applicants respectfully request that the rejection of claims 2, 25, 27, 29, 31, 33, and 34 under 35 U.S.C. § 103 be withdrawn,

CONCLUSIONS

On the basis of the above remarks, this application is believed to be in condition for allowance. Accordingly, reconsideration of this application and its allowance are respectfully requested.

A request for a Three (3) Month Extension of Time, up to and including July 29, 2003 is included herewith. Pursuant to 37 C.F.R. § 1.136(a)(3), the Examiner is authorized to charge any fee under 37 C.F.R. § 1.17 applicable in the instant, as well as in future communications, to Deposit Account No. 50-0943. Such an authorization should be treated as a constructive petition for extension of time in the concurrent as well as future replies, regardless of whether a separate petition is included.

The Examiner is encouraged to call the undersigned at (305) 575-6075or Sr. IP Counsel, Simona Levi-Minzi (Reg. No.: 43,750) at (305) 575-6061 to facilitate prosecution.

Respectfully submitted,
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